The Pharmacology of Autonomic Failure: From Hypotension to Hypertension

Italo Biaggioni

Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Vanderbilt University, Nashville, Tennessee

Abstract

Primary neurodegenerative autonomic disorders are characterized clinically by loss of autonomic regulation of blood pressure. The clinical picture is dominated by orthostatic hypotension, but supine hypertension is also a significant problem. Autonomic failure can result from impairment of central autonomic pathways (multiple system atrophy) or neurodegeneration of peripheral postganglionic autonomic fibers (pure autonomic failure, Parkinson’s disease). Pharmacologic probes such as the ganglionic blocker trimethaphan can help us in the understanding of the underlying pathophysiology and diagnosis of these disorders. Conversely, understanding the pathophysiology is crucial in the development of effective pharmacotherapy for these patients. Autonomic failure patients provide us with an unfortunate but unique research model characterized by loss of baroreflex buffering. This greatly magnifies the effect of stimuli that would not be apparent in normal subjects. An example of this is the discovery of the osmopressor reflex: ingestion of water increases blood pressure by 30–40 mm Hg in autonomic failure patients. Animal studies indicate that the trigger of this reflex is related to hypo-osmolality in the portal circulation involving transient receptor potential vanilloid 4 receptors. Studies in autonomic failure patients have also revealed that angiotensin II can be generated through noncanonical pathways independent of plasma renin activity to contribute to hypertension. Similarly, the mineralocorticoid receptor antagonist eplerenone produces acute hypotensive effects, highlighting the presence of non-nuclear mineralocorticoid receptor...
pathways. These are examples of careful clinical research that integrates pathophysiology and pharmacology to advance our knowledge of human disease.

I. Introduction

A. Overview of Normal Cardiovascular Autonomic Regulation

The autonomic nervous system provides modulatory influence on a number of organ systems. It plays a critical role in the regulation of cardiovascular function, providing instantaneous feedback for blood pressure (BP) homeostasis. Nowhere is there more evidence than in patients with primary forms of autonomic failure. The clinical picture in these patients is dominated by profound and disabling orthostatic hypotension (a drop in BP on standing). Pharmacological probes have helped us understand the pathophysiology of these disorders, and, conversely, these patients provide us with an unfortunate but unique human model to understand cardiovascular autonomic pathophysiology. This review complements others on this topic (Shibao et al., 2006b, 2012, 2013; Biaggioni, 2008; Jordan et al., 2015) by focusing on the pharmacology relevant to the pathophysiology and treatment of BP abnormalities present in patients with autonomic failure: orthostatic hypotension and supine hypertension.

B. The Baroreflex

BP is modulated second by second by a feedback loop that constitutes the baroreflex. A blood volume overload or an increase in BP is sensed by low-pressure receptors located in the heart and great veins, and by high-pressure receptors in the carotid sinus, respectively; this information is relayed to the nucleus tractus solitarii (NTS) of the brainstem, where it is integrated. The NTS provides excitatory input to modulate both sympathetic and parasympathetic function; stimulation of the NTS activates the caudal ventrolateral medulla, which provides inhibitory input for the rostroventrolateral medulla, where sympathetic tone is thought to be generated; at the same time, stimulation of the NTS activates the dorsal vagal nucleus of the vagus and nucleus ambiguus, where parasympathetic activity is generated. Thus, an increase in BP leads to activation of arterial baroreceptors and activation of the NTS, which induces parallel inhibition of sympathetic tone (through inhibition of the rostroventrolateral medulla), activation of parasympathetic tone (through activation of the dorsal vagal nucleus of the vagus). Sympathetic efferent fibers run through the intermedialateral columns of the spinal cord and make their first synapse in paravertebral autonomic ganglia, where postganglionic fibers originate to innervate the vasculature and the heart. Vagal fibers run through the vagus nerve and synapse in ganglia located within target organs. Thus, the initial increase in BP ultimately leads to inhibition of sympathetic tone to the vasculature (resulting in vasodilation) and to the heart (resulting in a decrease in cardiac output), and activation of parasympathetic tone to the heart (leading to a decrease in heart rate). These actions restore BP to baseline values. Thus, the baroreflex provides continuous and instantaneous regulation of BP.

C. Pathophysiology of Orthostatic Hypotension and Autonomic Failure

Gravitational forces exerted by standing result in pooling of up to 700 ml blood in the legs and lower abdomen, venous return decreases resulting in a reduction in stroke volume and cardiac output, and a transient decrease in BP; these changes are normally compensated by baroreflex-mediated sympathetic activation that induces splanchnic venoconstriction to partially restore venous return, increases heart rate and cardiac output, and induces systemic vasoconstriction to restore BP.

These autonomic pathways are essential for the maintenance of upright posture, and their failure results in orthostatic hypotension. Notably, heart rate does not increase appropriately in response to the drop in BP, evidence that normal counter-regulatory mechanisms are lost.

There are numerous diseases that can cause impaired autonomic function, but the most severe cases are seen in primary neurodegenerative diseases of the autonomic nervous system that result in pathologic lesions at different levels of baroreflex pathways. All have in common the deposit of the neuronal protein α-synuclein, but differ in their distribution. In multiple system atrophy (MSA), these deposits form cytoplasmic inclusion in glia located in central autonomic pathways, whereas in pure autonomic failure (PAF) they form Lewy bodies in peripheral noradrenergic fibers. Paradoxically, in Parkinson’s disease (PD) the autonomic lesions are also peripheral and indistinguishable from PAF, but, in addition, there are Lewy bodies in basal ganglia responsible for the movement disorder (i.e., the movement disorder is central, but the autonomic lesion is peripheral). In either case, the patients lose baroreflex mechanisms and are unable to compensate the orthostatic venous pooling with reflex sympathetic activation, and therefore develop profound orthostatic hypotension.

ABBREVIATIONS: BP, blood pressure; CNS, central nervous system; LAAAD, L-araomatic-ami-no-acid decarboxylase; L-NMMA, L-NO-monomethyl arginine; MR, mineralocorticoid receptor; MSA, multiple system atrophy; NET, norepinephrine transporter; NO, nitric oxide; NTS, nucleus tractus solitarii; PAF, pure autonomic failure; PD, Parkinson’s disease; rHuEPO, recombinant human erythropoietin.
D. Ganglionic Blockade as a Pharmacological Probe

To Understand Autonomic Failure

As mentioned above, the autonomic lesion in PAF and PD is peripheral, with neurodegeneration of postganglionic efferent noradrenergic fibers. In contrast, in patients with multiple system atrophy, the lesion is in central nervous system (CNS) autonomic nuclei, whereas postganglionic noradrenergic fibers appear to be intact. Biochemically, this is translated in very low levels of plasma norepinephrine in PAF (Goldstein et al., 1989) and lack of uptake of labeled catechols in the heart (Goldstein et al., 1997). Conversely, plasma norepinephrine levels are near normal in MSA, and cardiac catechol uptake is intact.

It is possible also to make this distinction pharmacologically, using a ganglionic blocker. Neurotransmission at the level of the autonomic ganglia is mediated by presynaptic release of acetylcholine, which then activates postsynaptic N-cholinergic receptors. Trimethaphan is an antagonist of these receptors, and i.v. infusion of this drug results in acute and complete interruption of all sympathetic and parasympathetic traffic. In patients with MSA ganglionic blockade interrupts their residual sympathetic tone and decreases BP. In contrast, in patients with peripheral postganglionic lesions (PAF) ganglionic blockade has no significant effect on BP (Shannon et al., 1997; Jordan et al., 2015).

Ganglionic blockade, by acutely removing autonomic function, can also be used in humans to infer what effect tonic sympathetic tone has on physiologic and pathologic processes. This is analogous to the use of the ganglionic blocker hexamethonium in animals (Iida, 1999). Thus, trimethaphan has been used to infer the contribution of sympathetic tone to hypertension (Diedrich et al., 2003) and the metabolic defects associated with obesity hypertension (Shibao et al., 2007b), including insulin resistance (Gamboa et al., 2014).

E. Autonomic Failure as a Model To Understand Pathophysiology

Baroreflex pathways are interrupted in autonomic failure patients (MSA and PAF), regardless of the level of the lesion. These patients, therefore, lack baroreflex buffering, and this can unmask the effect of drugs or even physiologic processes that may not be apparent in normal individuals. The discovery of the osmopressor reflex is an example of these phenomena. Acute ingestion of water (500 cc) triggers a dramatic pressor response in patients with autonomic failure, with an average increase in BP of almost 40 mm Hg, and as high as 70 mm Hg (Jordan et al., 1999a). A combination of animal and human studies suggests that water absorption induces a hypo-osmolar stimuli in the portal circulation, likely involving activation of transient receptor potential vanilloid 4 (McHugh et al., 2010), which triggers a sympathetic reflex (Jordan et al., 2000) that increases BP. This effect is apparent in autonomic failure because it is unopposed by the absence of baroreflex buffering. Evidence of this osmopressor reflex has subsequently been found in normal and hypertensive subjects as an increase in sympathetic nerve traffic and a modest increase in BP (Scott et al., 2001; Callegaro et al., 2007).

Trimethaphan also allows us to eliminate baroreflex pathways that would normally restrain the cardiovascular effects of agonist or antagonists. As an example, administration of the nitric oxide (NO) inhibitor L-NMMA produces a significant but relatively minor increase in BP in humans (of about 6 mm Hg). The increase in BP, due to removal of tonic NO-induced vasodilation, is counteracted by baroreceptor loading with sympathetic inhibition and partial restoration of BP. If baroreflex pathways are eliminated with trimethaphan, i.v. infusion of L-NMMA results in an increase in BP of 20–30 mm Hg (Gamboa et al., 2007, 2012). These findings are in agreement with the significant pressor response induced by L-NMMA in patients with baroreflex impairment due to severe autonomic failure (Gamboa et al., 2008). Thus, ganglionic blockade with trimethaphan can be used to unmask the real contribution of NO (and other autacoids) to BP modulation in humans.

II. Targeting Venous Compliance in the Treatment of Orthostatic Hypotension

As discussed above, gravitational venous pooling is the initial mechanism leading to orthostatic hypotension. Most of the venous pooling induced by standing occurs in the splanchnic circulation (Diedrich and Biaggioni, 2004). The splanchnic venous circulation is a highly compliant venous bed that normally stores ~25% of the blood volume (Rowell et al., 1972), and receives up to 25% of the resting cardiac output (Gelman, 2008). It represents the largest blood volume reservoir in the body and is highly innervated by sympathetic nerves. Veins of the extremities, in contrast, are less compliant and have relatively insignificant sympathetic innervation; thus, their role as blood volume reservoir is relatively minimal (Gelman, 2008). Consistent with this, compression of venous capacitance beds in the lower body has been shown in laboratory settings to improve upright BP and orthostatic symptoms in patients with primary autonomic failure by increasing stroke volume and cardiac output (Smit et al., 2004). Abdominal venous compression was significantly more effective than leg compression in improving standing BP, presumably because of the smaller volume reservoir in legs compared with the larger capacity of the abdominal vascular bed (Denq et al., 1997; Smit et al., 2004; Protheroe et al., 2011).

From these observations, it follows that drugs that reduce splanchnic venous compliance would be effective in treating orthostatic hypotension. Unfortunately, difficulties in measuring splanchnic compliance in humans

Pharmacology of Autonomic Failure

55

From these observations, it follows that drugs that reduce splanchnic venous compliance would be effective in treating orthostatic hypotension. Unfortunately, difficulties in measuring splanchnic compliance in humans
have limited our knowledge of treatments that can target this problem. There is only indirect information about the effect of medications used to treat orthostatic hypotension on the venous circulation. Midodrine improves venous return in a dog model of neurogenic orthostatic hypotension (ganglionic blockade with hexamethonium) presumably by producing splanchnic venoconstriction (Yamazaki et al., 1987). It is also an effective vasoconstrictor of isolated human veins (Thulesius et al., 1979). However, the pressor effects of midodrine in autonomic failure patients appear to be related mostly to an increase in arterial peripheral vascular resistance (Schrage et al., 2004; Duschek et al., 2009). Another example of a medication that can work at least partially through constriction of the venous circulation is octreotide, a somatostatic analog that inhibits the release of a number of gastrointestinal vasodilating peptides. Octreotide produces significant increases in BP in patients with autonomic failure and reduces orthostatic hypotension (Hoeldtke and Israel, 1989). Octreotide reduces splanchnic capacitance and improves venous return in a dog model of orthostatic hypotension (Wong and Sheriff, 2011). In healthy young women, octreotide improved orthostatic tolerance in relation to a reduction in splanchnic arterial vasoconstriction (Jarvis et al., 2012). It is likely that octreotide reduces splanchnic capacitance in humans, but, to the best of our knowledge, this has not been tested; arguably, the best model for such a study would be autonomic failure patients.

III. Pharmacology of Volume Expansion

If impaired venous return and decreased stroke volume are important contributors to orthostatic hypotension, an overall increase in blood volume may be beneficial. The mineralocorticoid fludrocortisone has been used to stimulate sodium reabsorption and increase extracellular water. More recently, recombinant erythropoietin has been used to increase red cell mass, resulting in a more selective increase in intravascular volume. However, as discussed below, it is not clear whether the beneficial effects of these drugs are related to their effect on volume expansion.

A. Fludrocortisone

Fludrocortisone produces an expansion of interstitial volume. The increase in plasma volume is a nonselective product of this increase and is only transient; it peaks during the first 2 weeks of treatment, but then plasma volume returns to baseline values (mineralocorticoid escape). Persistence of the pressor effects of fludrocortisone appears to be related to potentiation of the effects of norepinephrine and angiotensin II (Hickler et al., 1959; van Lieshout et al., 2000). Furthermore, we recently found that mineralocorticoid receptor (MR) blockade with eplerenone acutely lowers BP in autonomic failure patients, suggesting the presence of pressor effects of MR activation unrelated to volume regulation (Arnold et al., 2016). It is possible, therefore, that fludrocortisone’s activation of this putative MR pathway contributes to its pressor effect.

B. Erythropoietin

Patients with severe autonomic failure have a high incidence of anemia, up to 38% in some series (Biaggioni et al., 1994a). The anemia of autonomic failure is associated with impaired compensatory erythropoiesis with inappropriately low serum erythropoietin, and can be corrected with treatment with recombinant human erythropoietin (rHuEPO) (Hoeldtke and Streeter, 1993; Biaggioni et al., 1994a; Perera et al., 1995). The severity of anemia is typically modest, and its treatment with rHuEPO would not be justified clinically, but the increase in red cell mass is associated with increased BP and improved orthostatic tolerance. This pressor response is expected because it is a well-documented side effect of rHuEPO treatment in chronic renal failure patients. rHuEPO has the theoretical advantage that it selectively increases intravascular volume, compared with the transient increase in interstitial volume induced by fludrocortisone. It is not clear, however, that the increase in intravascular volume is the main mechanism by which rHuEPO increases BP. Erythropoietin increases BP in animals and patients even if correction of anemia is prevented (Vaziri, 2001).

IV. Replacing Noradrenergic Stimulation in the Treatment of Orthostatic Hypotension

Fludrocortisone produces an expansion of interstitial volume. The increase in plasma volume is a nonselective product of this increase and is only transient; it peaks during the first 2 weeks of treatment, but then plasma volume returns to baseline values (mineralocorticoid escape). Persistence of the pressor effects of fludrocortisone appears to be related to potentiation of the effects of norepinephrine and angiotensin II (Hickler et al., 1959; van Lieshout et al., 2000). Furthermore, we recently found that mineralocorticoid receptor (MR) blockade with eplerenone acutely lowers BP in autonomic failure patients, suggesting the presence of pressor effects of MR activation unrelated to volume regulation (Arnold et al., 2016). It is possible, therefore, that fludrocortisone’s activation of this putative MR pathway contributes to its pressor effect.

B. Erythropoietin

Patients with severe autonomic failure have a high incidence of anemia, up to 38% in some series (Biaggioni et al., 1994a). The anemia of autonomic failure is associated with impaired compensatory erythropoiesis with inappropriately low serum erythropoietin, and can be corrected with treatment with recombinant human erythropoietin (rHuEPO) (Hoeldtke and Streeter, 1993; Biaggioni et al., 1994a; Perera et al., 1995). The severity of anemia is typically modest, and its treatment with rHuEPO would not be justified clinically, but the increase in red cell mass is associated with increased BP and improved orthostatic tolerance. This pressor response is expected because it is a well-documented side effect of rHuEPO treatment in chronic renal failure patients. rHuEPO has the theoretical advantage that it selectively increases intravascular volume, compared with the transient increase in interstitial volume induced by fludrocortisone. It is not clear, however, that the increase in intravascular volume is the main mechanism by which rHuEPO increases BP. Erythropoietin increases BP in animals and patients even if correction of anemia is prevented (Vaziri, 2001).

IV. Replacing Noradrenergic Stimulation in the Treatment of Orthostatic Hypotension

Neurogenic orthostatic hypotension is due, in its simplest concept, to a failure of noradrenergic stimulation that normally occurs in the upright posture. It follows that a potential treatment is the administration of noradrenergic agonists. The beneficial effect of this approach can be attributed mostly to α-receptor activation, rather than β-receptor stimulation. In general this approach increases both supine and upright BP (and often the increase in supine BP is greater than the increase in upright BP). Hence, orthostatic hypotension (the difference between supine and upright BP) is often not improved, but rather upright BP is increased enough to prevent the fall in cerebral blood flow responsible for orthostatic symptoms.
A. Midodrine

Midodrine is a prodrug; it is rapidly and almost completely absorbed following oral administration and metabolized by enzymatic hydrolysis to the selective $\alpha_1$ agonist desglymidodrine. Peak concentrations of the active metabolite are reached in about 1 hour. The elimination half-life of the active metabolite is about 3 hours (McTavish and Goa, 1989). Clinical studies have shown that midodrine improves upright BP in patients with orthostatic hypotension (Kaufmann et al., 1988; Jankovic et al., 1993; Low et al., 1997). The pharmacological actions of midodrine are those of a selective $\alpha_1$ agonist of both $\alpha_{1A}$ and $\alpha_{1B}$ receptor subtypes. Hemodynamically, this translates to vasoconstriction, increase in peripheral vascular resistance, and elevated BP without an increase in heart rate. $\alpha$-Receptor activation can also induce venoconstriction, but it is not clear whether this effect contributes to the improvement in orthostatic tolerance. The side effects are also explained by activation of $\alpha$-receptors: piloerection, sensation of coldness, and urinary retention. Desglymidodrine diffuses poorly across the blood-brain barrier, and is therefore not associated with central nervous system effects.

B. Droxidopa

L-threo-3,4-dihydroxyphenylserine (droxydopa) is a synthetic catechol that is converted in the body to norepinephrine, via decarboxylation catalyzed by L-aromatic amino-acid decarboxylase (LAAAD; also known as dopa decarboxylase). This is the same enzyme that converts levodopa, used in the treatment of PD, to dopamine. Inhibitors of LAAAD that do not cross the blood-brain barrier are routinely given in combination with levodopa in PD patients to increase CNS conversion to dopamine and prevent peripheral effects like nausea.

Peak plasma droxidopa levels occur at about 3 hours, followed by a monoexponential decline with a half-time of 2–3 hours. Plasma levels of its main neuronal metabolite, dihydroxyphenylglycol, increase in parallel, but at much lower concentrations than the parent compound. Droxidopa increases BP in patients with neurogenic orthostatic hypotension (Freeman et al., 1999; Mathias et al., 2001; Kaufmann et al., 2003) and improves orthostatic tolerance (Kaufmann et al., 2014; Biaggioni et al., 2015; Hauser et al., 2015). Coadministration of high doses of the peripheral LAAAD inhibitor carbidopa prevents the BP effects of the droxidopa (Kaufmann et al., 2003), indicating that droxidopa increases BP by augmenting norepinephrine outside the brain.

Droxidopa is particularly effective in the treatment of dopamine-$\beta$-hydroxylase deficiency, a rare congenital disorder characterized by the lack of the enzyme that converts dopamine to norepinephrine (Biaggioni and Robertson, 1987; Man in ’t Veld et al., 1988). Droxidopa bypasses the enzymatic defect and restored norepinephrine levels.

V. Harnessing Residual Sympathetic Tone To Treat Orthostatic Hypotension

An alternative to the use of direct $\alpha$ agonists is to induce the release of endogenous norepinephrine by increasing residual sympathetic tone that may still be present in these patients. This has the theoretical advantage that it will result in a more physiological restoration of noradrenergic function, with the potential to preferentially improve BP during upright posture, when residual sympathetic activity would be greater. Likewise, in theory this approach should be more effective in patients with impaired central autonomic pathways but intact peripheral noradrenergic fibers (MSA), than in patients with neurodegeneration of peripheral noradrenergic fibers (PAF, PD). In practice, even patients with peripheral autonomic failure have some degree of residual sympathetic function, and even modest stimulation of norepinephrine release can result in significant increases in BP due to activation of upregulated adrenergic receptors unopposed because of the absence of baroreflex buffering.

A. Pyridostigmine

Pyridostigmine is an inhibitor of cholinesterase, the enzyme that catalyzes the hydrolysis of the neurotransmitter acetylcholine into choline and acetic acid, a reaction that occurs in the cholinergic synapse that essentially terminates the actions of acetylcholine. Pyridostigmine therefore facilitates cholinergic neurotransmission, and, because acetylcholine is the neurotransmitter in autonomic ganglia, pyridostigmine can increase residual sympathetic tone. In this regard, its actions are opposite those of trimethaphan discussed above (see Ganglionic Blockade as a Pharmacological Probe To Understand Autonomic Failure).

In the supine position, when sympathetic tone is normally low, neurotransmission at the level of sympathetic ganglia is reduced and pyridostigmine would have less of an effect. In contrast, its effects are more prominent during standing, when traffic through sympathetic ganglia is normally increased. This offers the theoretical advantage of preferentially increasing upright BP in patients with autonomic failure and in proportion to their orthostatic needs. Most other pressor agents increase supine BP more than standing BP, and worsening of supine hypertension can limit their use. This adverse effect would be minimized with pyridostigmine.

Indeed, in clinical trials pyridostigmine preferentially improved upright compared with supine BP in autonomic failure patients (Singer et al., 2003, 2006). The increase in upright BP was rather modest, only 4 mm Hg higher in the pyridostigmine group compared with the placebo group 2 hours after drug administration. Nonetheless, this modest increase in upright BP was associated with a significant improvement in orthostatic symptoms. In theory, patients with residual sympathetic tone (i.e., MSA) should be more responsive to enhancement of
sympathetic ganglia neurotransmission compared with patients with peripheral neuropathy (i.e., PAF or PD). This, however, was not found, possibly because of the small number of patients in each group. Nonetheless, patients with relatively preserved baroreflex gain had a greater response, supporting the notion that the response to pyridostigmine is proportional to the degree of residual sympathetic tone. It is likely that this treatment is effective in less severe patients with residual sympathetic tone.

B. Yohimbine

Yohimbine is an indole alkaloid isolated from the bark of the *Pausinystalia yohimbe* tree. It is a selective $\alpha_2$ antagonist. As such it has opposite pharmacologic and cardiovascular effects of the partial $\alpha_2$ agonist clonidine; centrally yohimbine stimulates sympathetic outflow, and, in the periphery, it enhances the release of norepinephrine from adrenergic nerve fibers by antagonizing presynaptic $\alpha_2$-adrenergic receptors that normally inhibit norepinephrine release. It appears that both central and peripheral actions of yohimbine contribute to its cardiovascular effects. Grossman et al. (1991) found in normal volunteers that steady-state infusion of yohimbine produced a 16% increase in mean arterial BP, 8% increase in heart rate, and 67% increase in forearm vascular resistance. Of interest, the increase in muscle sympathetic nerve activity (by 73%) was much smaller than the increase in forearm norepinephrine spillover (by 337%), suggesting that blockade of inhibitory presynaptic $\alpha$ receptors resulting in stimulation of norepinephrine release contributes to the increase in BP induced by yohimbine.

The pressor effects of yohimbine are seen in autonomic failure patients at doses that would have negligible effects in normal subjects (Biaggioni et al., 1994b). In contrast, yohimbine has no effect in patients with dopamine $\beta$-hydroxylase deficiency unable to synthesize norepinephrine (Biaggioni et al., 1994b). Thus, yohimbine requires norepinephrine synthesis and release to act; conversely, it can be used to harness the residual sympathetic tone that is present even in patients with severe forms of autonomic failure. As expected, yohimbine increases BP more in patients with MSA and greater residual sympathetic tone compared with PAF, but there is significant overlap between groups (Shannon et al., 2000).

C. Atomoxetine

The norepinephrine transporter (NET) is located in the presynaptic neuron to reuptake norepinephrine from the synapse, thus contributing to the termination of the actions of norepinephrine. Atomoxetine is a selective blocker of NET and, therefore, potentiates the effect of synaptically released norepinephrine by increasing neurotransmitter concentrations in the neuroeffector junction. Increasing norepinephrine in peripheral noradrenergic fibers would increase BP. Conversely, in the CNS an increase in norepinephrine will activate central $\alpha_2$-adrenergic receptors that have a clonidine-like sympatholytic effect. In normal subjects these effects counteract each other, and no significant increase in BP is observed (Essler et al., 1991; Birkenfeld et al., 2005).

These contrasting effects of NET blockade can be unmasked in humans by studying patients with distinct forms of autonomic impairment; the peripheral pressor effects of NET blockade should be apparent in patients with intact peripheral sympathetic fibers (MSA), but not in patients with peripheral autonomic denervation (PAF). Indeed, atomoxetine acutely increased systolic BP by about 50 mm Hg in patients with central autonomic failure, but by less than 5 mm Hg in patients with severe peripheral autonomic failure (Shibao et al., 2007c). Subsequent studies have shown that atomoxetine can also increase BP in PAF patients with less severe autonomic failure (Ramirez et al., 2014).

When compared with midodrine at doses that produce the same increase in seated BP, atomoxetine produced a greater increase in upright BP (Ramirez et al., 2014). This is consistent with the concept that atomoxetine, as well as other therapies that harness residual sympathetic tone, provides a more physiologic approach to treat orthostatic hypotension.

The response to these drugs can provide insight about the pathophysiology of these disorders. Clonidine reduces BP in MSA patients because of a reduction in their residual sympathetic tone (Shibao et al., 2006a), as determined by a reduction in plasma norepinephrine (Young et al., 2006). This implies that central autonomic pathways involving postsynaptic activation of $\alpha_2$-adrenergic receptors are preserved in MSA. In contrast, tonic presynaptic release of norepinephrine in the CNS that normally decreases sympathetic tone appears to be impaired given that atomoxetine does not have this clonidine-like effect. This leaves unopposed the peripheral pressor actions of atomoxetine, which depends on residual sympathetic outflow with tonic release of norepinephrine, known to be preserved in MSA.

VI. The Hypertension of Autonomic Failure

In clinical practice, BP is routinely measured in the seated position, and most patients with autonomic failure will have a normal seated BP. It is not surprising that the diagnosis of orthostatic hypotension is delayed until their clinical picture is dominated by disabling orthostatic hypotension. Likewise, supine hypertension is also overlooked, even though over half of patients with autonomic failure have this problem. The prevalence of hypertension is similar to what we would expect...
in this age group. Given their absent baroreflex function, it is not surprising that they are not able to compensate, not only for the drop in BP on standing, but also for the mechanisms that drive hypertension with aging. It is not clear, however, whether the supine hypertension of autonomic failure is simply the unmasking of essential hypertension, or if these patients develop unique pathophysiological mechanisms of hypertension.

The supine hypertension of autonomic failure can be severe [BP as high as 230/140 mm Hg has been described (Shannon et al., 1997)] and associated with end-organ damage, including left ventricular hypertrophy (Vaganeasucu et al., 2000; Maule et al., 2006) and impaired renal function (Garland et al., 2009). Autonomic failure patients have arterial stiffness and hypertensive heart disease of similar magnitude as seen in patients with essential hypertension with comparable BP values (Milazzo et al., 2015). Supine hypertension may be associated with long-term end-organ damage, but it can also contribute to orthostatic hypotension. Supine hypertension leads to pressure diuresis as a renal compensatory mechanism to normalize BP. This translates as increased nighttime diuresis (nocturia); patients lose on average 1 L urine overnight due to this mechanism (Okamoto et al., 2009).

Hemodynamic studies suggest that supine hypertension is mediated by an increase in systemic vascular resistance (Kronenberg et al., 1990); cardiac output is not increased, and total blood volume is similar in patients with or without supine hypertension (Shannon et al., 1997). Supine hypertension is driven by their residual sympathetic activity in MSA patients because BP is normalized with ganglionic blockade with trimethaphan (Shannon et al., 2000). In patients with PAF, supine hypertension is associated also with increased systemic vascular resistance (Kronenberg et al., 1990), but does not decrease with ganglionic blockade, consistent with the low sympathetic tone that these patients have (Shannon et al., 2000). It remains unclear what vasoconstrictive mechanisms drive supine hypertension in PAF. This is another clinical example in which their response to pharmacological probes can help define the underlying pathophysiology of this disease.

A. Targeting Residual Sympathetic Tone

Because hypertension is driven by residual sympathetic tone in MSA, it is not unexpected that clonidine decreases BP by about 30 mm Hg in these patients and reduces their nocturnal natriuresis (Shibao et al., 2006a). Surprisingly, clonidine can also lower BP in in PAF, probably because they have some residual sympathetic tone. In contrast, at higher doses clonidine can increase BP in patients with severe PAF and low residual sympathetic, probably because of activation of vascular $\alpha_2$ adrenergic receptors.

B. The Renin-Angiotensin Aldosterone System in Autonomic Failure

The renin-angiotensin aldosterone system is widely recognized as an important contributor to the development of essential hypertension, primarily through the actions of angiotensin II at AT$_1$ receptors to stimulate vasoconstriction, baroreflex dysfunction, and aldosterone release. Initial studies had suggested that the renin-angiotensin aldosterone system plays little role in BP regulation in autonomic failure. These patients have very low and often undetectable levels of plasma renin activity, blunted renin responses to postural and pharmacologic stimuli, and loss of renin immunoreactive cells in autopsied kidneys (Biaggioni et al., 1993). However, more recent studies in autonomic failure patients found circulating angiotensin II levels that were paradoxically elevated compared with healthy subjects, despite low and often undetectable plasma renin activity (Arnold et al., 2013). These findings raise the possibility that renin-independent mechanisms are involved in the formation of angiotensin II in autonomic failure. Consistent with this, AT$_1$ receptor blockade with losartan, but not angiotensin converting enzyme inhibition with captopril, effectively lowered overnight supine BP (Arnold et al., 2013). Taken together, these results suggest that angiotensin II, produced through noncanonical pathways, contributes to supine hypertension in autonomic failure.

Aldosterone levels are also normal in these patients, suggesting that downstream renin-angiotensin pathways are intact in autonomic failure. Recent studies indicate that MR antagonism with eplerenone acutely lowered BP in patients with autonomic failure and supine hypertension (Arnold et al., 2016). Maximal hypotensive effects were seen about 8 hours after a single dose of eplerenone. Classic activation of the MR results in translocation of the ligand-receptor complex to the nucleus, where it binds hormone response elements in the promoter region of target genes to stimulate transcription (Fejes-Toth et al., 1998). These pathways would not explain the acute hypotensive effects of eplerenone in autonomic failure. Recently, activation of cell surface or cytosolic MR has been shown to elicit nongenomic rapid effects of aldosterone, including vasoconstriction and sympathetic activation (Funder, 2010). In addition, Ang II can activate vascular MR, through direct binding or indirectly through AT$_1$ receptor transactivation, to induce vasoconstriction, arterial stiffness, and oxidative stress (Jaffe and Mendelsohn, 2005; Rautureau et al., 2011).

C. Nitric Oxide and Autonomic Failure

As described above (see Ganglionic Blockade as a Pharmacological Probe To Understand Autonomic Failure), hypertension in PAF is not primarily due to residual sympathetic tone, raising the possibility that hormonal or metabolic factors are involved. NO is thought to be an important modulator of BP. Inhibition
of NO synthesis with L-NMMA results in a 30 mm Hg increase in BP in normal subjects in whom the restraining effect of the baroreflex was eliminated with ganglionic blockade (Gamboa et al., 2007). Impaired NO function could be proposed to contribute to the supine hypertension in PAF. However, current evidence suggests that PAF patients have an increase in NO function (Gamboa et al., 2008); NO synthesis inhibition with L-NMMA produced a greater increase in BP in autonomic failure compared with normal subjects. Conversely, autonomic failure patients have an exaggerated depressor response to sildenafil, a phosphodiesterase inhibitor that potentiates NO signal transduction.

Nebivolol is a selective $\beta_1$-adrenergic receptor blocker, and is considered a third-generation $\beta$-blocker with unique vasodilatory actions (Gao and Vanhoutte, 2012). It is proposed that augmentation of NO bioavailability underlies this vasodilatory effect (Bowman et al., 1994; Kubli et al., 2001; Dessy et al., 2005). The magnitude and relative contribution of NO-dependent vasodilation to the BP-lowering effect of nebivolol, however, are not known. In this regard, patients with autonomic failure provide a unique model to examine the role of NO potentiation in the cardiovascular effects of nebivolol. First, these patients lack autonomically mediated baroreflex buffering and therefore have exaggerated responses to most pressor and depressor agents (Jordan et al., 1998, 1999b, 1999c; Shibao et al., 2007a). Second, traditional $\beta$-blockers have no BP effect in these patients due to low $\beta$-adrenoreceptor tone (Man in’t Veld and Schalekamp, 1981; Man in’t Veld et al., 1982). Finally, these patients have an exaggerated response to NO-mediated vasodilation, as discussed previously (Gamboa et al., 2008). Indeed, nebivolol and sildenafil significantly reduced nighttime BP compared with placebo, whereas metoprolol had no effect. Furthermore, nebivolol decreased nighttime BP by $-44 \pm 13$ mm Hg in patients that responded to sildenafil while having no effect in nonresponders ($1 \pm 11$ mm Hg). Taken together, these results are consistent with the postulate that the decrease in BP by nebivolol in autonomic failure is related to NO mechanisms.

VII. Conclusions

Several lessons can be learned from patients with autonomic failure. Understanding the underlying pathophysiology of these disorders is crucial for their adequate diagnosis and pharmacological treatment. In this regard, pharmacological probes can help us understand the pathophysiology of autonomic failure. An example of this is the ganglionic blocker trimethaphan, which can be used to determine the amount of residual sympathetic tone that these patients have. This differentiates patients with MSA from PAF, in whom profound decreases in BP are seen in the former, but not the latter (see Ganglionic Blockade as a Pharmacological Probe To Understand Autonomic Failure). These observations also validate the use of trimethaphan as a pharmacologic probe to assess the importance of autonomic function in essential hypertension, insulin resistance, and other common conditions. It can also be used to eliminate the confounding effect of the baroreflex. Using this approach, one can unmask the real importance of, for example, NO; removal of NO with the NO synthase inhibitor L-NMMA revealed that, in the presence of trimethaphan, tonic NO function normally restrains BP by about 30 mm Hg in humans (see Autonomic Failure as a Model To Understand Pathophysiology). The hypotensive response to clonidine in MSA suggests that CNS nuclei pathways distal to origin of sympathetic tone are intact in these patients (see Targeting Residual Sympathetic Tone).

Conversely, autonomic failure patients provide us with an unfortunate but unique model devoid of baroreflex buffering. This greatly magnifies the effect of stimuli that would not be apparent in normal subjects. An example of this is the discovery of the osmopressor effect of water ingestion (Autonomic Failure as a Model To Understand Pathophysiology). Studies in autonomic failure patients have also revealed the importance of noncanonical generation of angiotensin II independent of plasma renin activity. Similarly, they reveal the acute hypotensive effects of MR blockade (see The Renin-Angiotensin Aldosterone System in Autonomic Failure). They also revealed the contribution of potentiation of NO function to the hypotensive actions of nebivolol (see Nitric Oxide and Autonomic Failure). These are examples of careful clinical research that integrates pathophysiology and pharmacology to advance our knowledge of human disease.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Biaggioni.

References


